## REMARKS

1. General Matters

1.1. We agree that claim 52 should be grouped with claim 51 for purpose of the election of species (D).

1.2. We have amended claim 11 to eliminate the reference to the figure.

2. Definiteness Issues (OA §2-4)

2.1. The Examiner rejects claims 1 and 66 by virtue of the language "or analogue thereof" (OA §2).

As exemplified by the Agrawal reference, there has been experimentation with modification of the CpG linkage. We generalized the linkage between the bases cytosine and guanine by our definition of "CxG". The term "or analogue thereof" is reference to the possibility of replacing cytosine with a cytosine analogue and/or guanine with a guanine analogue, as disclosed at page 25. We have added "wherein, in said analogue, (1) cytosine is replaced with a cytosine analogue which is a pyrimidine other than thymine or uracil, and/or (2) guanine is replaced with a guanine analogue which is a purine other than adenine".

2.2. The Examiner questions "strongly lipophilic" (OA §3). However, this term is precisely defined at page 49, line 27 to page 50, line 8. The cited methods (A)-(C) are at pp. 50-52. Note also the definition of "lipophilic group" at page 47, lines 20-23 and page 49, lines 12-13. It is thus quite clear what level is considered "strong".

3. Prior Art Issues (OA §5-7)

Claims 1-9, 11-14, 17-33, 35, 55-68, 72-81 and 100 were examined.

Claims 1-9, 11-14, 17-33, 35, 55-56, 59-63, 65-68, 72-81 and 100 are rejected as anticipated by Polson, USP 4,894,229.

Claims 1-9, 11-33, 35, 55-63, 65-68, 72-81 and 100 are rejected as anticipated by or obvious over Agrawal, USP

5,856,462.

Claims 1-9, 11-33, 35, 55-68, 72-81 and 100 are rejected as obvious over Krieg and Davis in view of Shea.

3.1. The Polson rejection argues that the claim reads on Polson's complete bacterial cells, which allegedly inherently comprise immunostimulatory molecules comprising at least one CxG molecule as well as covalently incorporated lipophilic groups.

Claim 1, as amended, distinguishes Polson by requiring that the immunostimulatory molecule be "isolated".

However, even without such amendment, the propriety of this rejection is doubtful. The CxG moieties are found only in intracellular molecules (DNA and RNA). Absent some showing that the cell is lysed to expose these molecules, it seems that administering the bacteria does not constitute administration of the intracellular DNA or RNA.

Moreover, it is not clear to us how the examiner is construing these CpG-containing molecules to also be comprising covalently incorporated lipophilic groups. The base, phosphate and sugar of DNA or RNA are all considered to be hydrophilic.

There are certainly other molecules in bacteria which comprise lipophilic groups, but such are not covalently linked to the CpG.

Consequently, we have presented new claim 107, which does not rely on "isolated" to distinguish Polson.

3.2. Agrawal teaches administration of "modified CpG"-containing oligonucleotides. According to col. 3-4, the purpose of the modification is to reduce the ability of the oligonucleotide to cause splenomegaly and platelet depletion when administered to a mammal.

Our claim 1 is directed to a method of stimulating the immune system. This does not appear to be Agrawal's purpose. Rather, Agrawal is contemplating antisense gene therapy (col. 3, lines 27-28 and 38-52), but with reduced side effects.

The Examiner has made no showing that Agrawal's "modified-CpG" contains oligonucleotides which would <u>necessarily</u> stimulate

the immune system, which would seem a prerequisite for a holding of inherent anticipation.

Agrawal teaches that his oligonucleotides are preferably about 12 to about 50 nucleotides, see col. 4, lines 22-24. There is no specific disclosure of any oligo shorter than a 12-mer, so that is another possible basis from distinction. Claim 1 has been amended to incorporate the limitation of claim 57 on the length of the oligonucleotide.

Several dependent claims further distinguish Agrawal:

Claim 3: While a "modified CpG" would seemingly satisfy the definition of "CxG", claim 3 requires unmodified CpG which distinguishes Agrawal.

Claim 9: Agrawal teaches the incorporation of "lipophilic groups" at col. 14, line 15, apparently as "additional substituents". There is no further delineation of the identity or purpose of these lipophilic groups. In general, disclosure of a genus ("lipophilic groups") does not anticipate a species (e.g., the elected lipophilic group "c", which has the structure -XR wherein X is -O-, -S- or -NH- and R is aliphatic, cp. claim 9 clause (c)).

Claims 78-81: There is no teaching of conjunctive administration of a pharmaceutical composition comprising an immunogen.

3.3. Krieg (IDS ref. AT) and Davis (IDS ref. BE) are cited for teaching stimulation of an immune response by means of a CpG-containing oligonucleotide. Krieg is cited by us at page 2, lines 27-31. For discussion of Davis (Wo98/18810), see page 2, line 32 to page 3, line 23. Note that we argued that Davis taught away from oligomers shorter than 8 bases being immunostimulatory. While we didn't say so, Krieg page 546 col. 2 also asserts that stimulatory activity was lost if the length were reduced below 8 bases.

Krieg and Davis are thus seemingly distinguished by claim 57:

> The method of claim 1 in which there are no more than seven nucleobases in each

oligonucleotide strand.

And cp. claim 58 ("no more than four nucleobases"). Claim 1 has been amended to incorporate the limitation of claim 57.

Shea (IDS ref. BT) is said to teach lipid-oligonucleotide conjugates with antiviral activity. There is no established correlation between antiviral activity and immunostimulatory activity.

Shea also teaches that the lipid-DNA complexes were 8-10 times more cell associated than unaltered DNA. There has also been no showing that the inactivity of the shorter oligonucleotides (per Davis) was attributable to limited cell uptake. Hence, Shea's finding would not have motivated the art to lipidate the shorter (presumably inactive) oligonucleotides.

Moreover, Shea's lipidated oligonucleotides were themselves long (at least 15-mers) and hence it cannot be inferred that lipidation would have improved uptake of the shorter oligos of our claim 57.

Respectfully submitted,

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